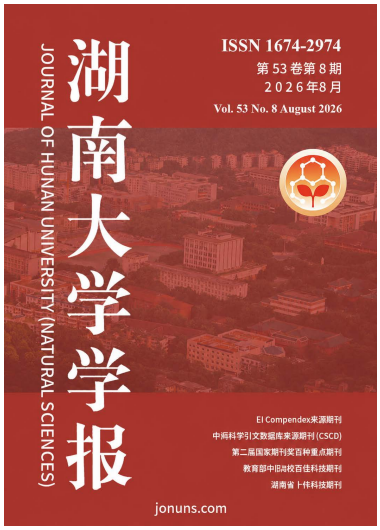

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Effects of Mesenchymal Stem Cell-Derived Secretome on Glycemic Control and Pancreatic Islet Morphology in Streptozotocin-Induced Diabetic Rats

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Abstract: Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia and progressive pancreatic islet dysfunction. The mesenchymal stem cell (MSC)-derived secretome has been investigated as a potential cell-free therapeutic approach because of its reported paracrine, anti-inflammatory, and tissue-reparative effects. This study evaluated the effects of MSC-derived secretome administration on day-28 random blood glucose levels and pancreatic islet morphology in streptozotocin (STZ)-induced diabetic rats. Twenty-one male Sprague–Dawley rats were randomly assigned to three groups: negative control, diabetic control, and secretome-treated diabetic groups (n = 7 per group). The treated group received 0.5 mL of umbilical cord MSC-derived secretome

intraperitoneally once weekly for three consecutive weeks, beginning on day 8 after STZ induction. Day-28 random blood glucose levels were analyzed using the Kruskal–Wallis test followed by Bonferroni-adjusted Mann–Whitney U tests. Pancreatic islet area was analyzed using one-way analysis of variance followed by Bonferroni-adjusted post hoc comparisons. Day-28 random blood glucose was lower in the secretome-treated diabetic group than in the diabetic control group (263.71 ± 122.29 vs. 423.00 ± 36.89 mg/dL; adjusted p = 0.0378). Pancreatic islet area differed among the three groups (p = 0.0043), with a significant difference between the negative control and diabetic control groups (p = 0.004). The difference between the diabetic control and secretome-treated diabetic groups was not statistically significant (p = 0.061). Qualitative examination of hematoxylin and eosin (H&E)-stained sections suggested better-preserved islet morphology in the treated group. These findings indicate lower day-28 random blood glucose following secretome treatment, while evidence for an improvement in pancreatic islet area remains inconclusive. The study does not establish β-cell regeneration.

Keywords: mesenchymal stem cell-derived secretome; streptozotocin-induced diabetes; random blood glucose; pancreatic islet morphology; Sprague–Dawley rats.

间充质干细胞来源分泌组对链脲佐菌素诱导的糖尿病大鼠血糖控制及胰岛形态的影响

摘要： 糖尿病是一种以持续性高血糖和胰岛功能逐渐受损为特征的慢性代谢性疾病。间充质干细胞（MSC）来源分泌组因具有已报道的旁分泌、抗炎和组织修复作用，被研究作为一种潜在的无细胞治疗方法。本研究评估了MSC来源分泌组对链脲佐菌素（STZ）诱导的糖尿病大鼠第28天随机血糖水平及胰岛形态的影响。21只雄性Sprague–Dawley大鼠被随机分为阴性对照组、糖尿病对照组和分泌组治疗的糖尿病组，每组7只。治疗组自STZ诱导后第8天开始，连续3周每周腹腔注射一次0.5 mL脐带MSC来源分泌组。采用Kruskal–Wallis检验及经Bonferroni校正的Mann–Whitney U检验分析第28天随机血糖水平；采用单因素方差分析及经Bonferroni校正的事后比较分析胰岛面积。分泌组治疗的糖尿病组第28天随机血糖水平低于糖尿病对照组（263.71 ± 122.29 mg/dL与423.00 ± 36.89 mg/dL；校正后 $p = 0.0378$）。三组间胰岛面积存在差异（$p = 0.0043$）；阴性对照组与糖尿病对照组之间的差异具有统计学意义（$p = 0.004$），但糖尿病对照组与分泌组治疗的糖尿病组之间的差异未达到统计学显著水平（$p = 0.061$）。对苏木精-伊红（H&E）染色切片的定性观察提示，治疗组的胰岛形态保存可能优于糖尿病对照组。研究结果表明，分泌组治疗后第28天随机血糖水平较低，但其是否能改善胰岛面积尚无定论。本研究不能证实β细胞再生。

关键词： 间充质干细胞来源分泌组；链脲佐菌素诱导的糖尿病；随机血糖；胰岛形态；Sprague–Dawley大鼠。

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia, which may lead to multisystem damage and severe long-term complications. Type 2 diabetes mellitus (T2DM) is the predominant form of diabetes and generally occurs in adulthood as a result of impaired insulin secretion by pancreatic β-cells and insulin resistance in peripheral tissues [1]. The International Diabetes Federation (IDF) has reported that diabetes is one of the fastest-growing global health challenges. According to the 2021 IDF data, Indonesia ranked fifth worldwide in the number of adults with diabetes, with an estimated prevalence of 10.8%, corresponding to approximately 19.5 million adult cases. Diabetes mellitus affects multiple organ systems and is commonly associated with microvascular complications, including retinopathy, nephropathy, and

neuropathy, as well as macrovascular complications related to cardiovascular disease [2,3].

In T2DM, impaired insulin production is closely associated with pancreatic β-cell dysfunction and insulin resistance. Chronic hyperglycemia and hyperlipidemia contribute to increased oxidative stress through the generation of reactive oxygen species (ROS), activation of pro-apoptotic signaling pathways, elevation of interleukin-1 (IL-1), and degradation of proinsulin mRNA. These processes cause β-cells to overcompensate, eventually leading to pancreatic β-cell dysfunction and injury. Histopathologically, this injury may be characterized by apoptosis, cellular degeneration, and structural alterations in the islets of Langerhans, resulting in a reduced pancreatic islet area [4,5].

Current management of diabetes mellitus includes lifestyle modification, dietary regulation, increased physical activity, and pharmacological interventions such as oral hypoglycemic agents and insulin therapy. However, these conventional treatments primarily focus on glycemic control and do not fully restore structural damage to pancreatic tissue. With advances in biomedical science, regenerative therapeutic approaches, particularly those involving mesenchymal stem cell (MSC)-derived secretome, have gained increasing research attention. MSC-derived secretome consists of various growth factors, cytokines, extracellular vesicles, and bioactive molecules that may exert anti-inflammatory, anti-apoptotic, and tissue-reparative effects [6,7]. These properties suggest that secretome may help protect pancreatic tissue from further injury and support pancreatic islet structural recovery [8].

MSC-derived secretome is expected to provide therapeutic effects comparable to those of stem cells, while offering a cell-free approach with potential advantages in terms of safety and clinical applicability. Previous studies have shown that stem cell-based therapies may improve insulin sensitivity, reduce inflammation, and support pancreatic β-cell preservation in experimental models of diabetes [7]. Wang et al. reported that adipose-derived stem cells (ASCs) improved insulin sensitivity and promoted pancreatic β-cell recovery in diabetic conditions [8]. Furthermore, Rini P.D. demonstrated that MSC-derived secretome increased the number of pancreatic β-cells in a murine model of type 1 diabetes mellitus [9].

Based on these findings, the present study investigated MSC-derived secretome as a potential therapeutic agent in an STZ-induced diabetic rat model. The bioactive components of the secretome may contribute to tissue-protective and paracrine effects in pancreatic islets. This study aimed to evaluate the effects of MSC-derived secretome administration on random blood glucose levels and pancreatic islet morphology in STZ-induced diabetic rats.

2. Methods

2.1 Study Design and Setting

This experimental study used male Sprague-Dawley rats to evaluate the effects of mesenchymal stem cell (MSC)-derived secretome administration on random blood glucose levels and pancreatic islet morphology following streptozotocin (STZ) induction. The study was conducted at the Animal Laboratory and Anatomical Pathology Laboratory, School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, Jakarta. The overall research period extended from October 2024 to November 2025. Activities conducted before ethical approval consisted exclusively of protocol development, literature review, laboratory preparation, and study planning and did not involve experimental animals. The ethics application for the animal study was submitted to the Research Ethics Committee of the School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia on 26 July 2025, and ethical approval was granted on 8 August 2025 (Approval No. 02/08/KEP-FKIKUAJ/2025). All procedures involving animals, including acclimatization, STZ induction, secretome administration, blood glucose measurement, euthanasia, and tissue collection, were initiated only after ethical approval had been granted. The animal experimental phase lasted five weeks (one week of acclimatization followed by four weeks of experimental observation) and was conducted entirely after 8 August 2025.

2.2 Experimental Animals

The study population consisted of male Sprague-Dawley rats aged approximately 8 weeks and weighing 250 ± 5 g. These rats were selected because of their relatively stable physiological characteristics and their common use as experimental models of diabetes mellitus. The inclusion criteria were healthy male Sprague-Dawley rats aged approximately 8 weeks and weighing 250 ± 5 g. For the diabetic groups, successful diabetes induction was defined as a random blood glucose level exceeding 200 mg/dL after STZ administration. Rats that became ill during the acclimatization period were excluded from the study, whereas rats that became ill or died during the experimental period were considered dropouts.

2.3 Sample Size and Group Allocation

The sample size was determined using the Degrees of Freedom (E) method for analysis of variance, using the formula $E = N - t$, where E is the error degrees of freedom, N is the total number of experimental animals, and t is the number of experimental groups. An E value between 10 and 20 was considered acceptable. The present study included three groups with seven rats per group ($N = 21$); therefore, $E = 21 - 3 = 18$. Because the calculated E

value was within the acceptable range, seven rats per group were considered adequate. A total of 21 rats were randomly allocated to the negative control group, diabetic control group, and secretome-treated diabetic group.

2.4 Acclimatization, Treatment Groups, and Secretome Administration

Before treatment, all rats were acclimatized for one week in standard cages with free access to food and water. After acclimatization, the rats were randomly divided into three groups. The negative control group received neither STZ induction nor secretome treatment and was maintained under standard conditions. The diabetic control group received STZ at 45 mg/kg body weight without secretome administration. The secretome-treated diabetic group received STZ at the same dose, followed by intraperitoneal administration of 0.5 mL MSC-derived secretome once weekly for three consecutive weeks, beginning on day 8 after STZ induction.

The secretome used in this study was an umbilical cord mesenchymal stem cell-derived secretome (UCMSC-Secretome) obtained as a prepared product from Regenic, PT Bifarma Adiluhung, Indonesia. The product was supplied as a sterile injection solution in a 1.5-mL presentation. According to the manufacturer's documentation, the secretome contains a mixture of bioactive substances, including growth factors, soluble proteins, chemokines, cytokines, nucleic acids, lipids, and extracellular vesicles. Manufacturer-provided quantitative characterization reported basic fibroblast growth factor (bFGF) at 89-144 pg/mL, transforming growth factor-beta 1 (TGF-β1) at 438-577 pg/mL, keratinocyte growth factor (KGF) at 70-75 pg/mL, hepatocyte growth factor (HGF) at 1152-1290 pg/mL, and procollagen I alpha 1 at 467-512 ng/mL. These concentration ranges were based on manufacturer testing data from 2020 to September 2023 for analytes within the limits of detection and quantification of the respective assays. Detailed information regarding MSC passage number, culture and conditioning conditions, secretome collection and processing procedures, storage conditions, and batch-specific characterization was not available in the documentation accessible to the authors and therefore could not be retrospectively verified.

2.5 Induction of Experimental Diabetes

Experimental diabetes was induced by a single intraperitoneal administration of STZ at 45 mg/kg body weight on day 1. Before STZ administration, the rats were fasted for 8-12 hours. STZ was freshly dissolved in 0.1 M citrate buffer at pH 4.5 before administration. Rats with random blood glucose levels exceeding 200 mg/dL after STZ administration were considered diabetic and were included in the diabetic groups. Because this protocol did not include a high-fat diet, nicotinamide administration, or direct assessment of insulin resistance, the model is referred to throughout this manuscript as an STZ-induced diabetic rat model rather than specifically as a type 2 diabetes mellitus model.

2.6 Blood Glucose Measurement

Random blood glucose levels were measured before STZ induction, daily during the first week after induction, and subsequently on days 14, 21, and 28 using a glucometer. Blood samples were obtained from the tail tip using a sterile blade, placed onto a glucometer strip, and recorded. Measurements obtained during the study were used to monitor the development and persistence of hyperglycemia. For the between-group statistical analyses reported in Tables 1-3, the day-28 random blood glucose measurement was used as the endpoint value.

2.7 Tissue Collection and Histological Preparation

On day 28, the rats were euthanized using a ketamine and xylazine mixture at doses of 70 mg/kg and 8 mg/kg body weight, respectively. The pancreas was then excised, washed with 0.9% NaCl, and fixed in 10% buffered formalin. Pancreatic tissue samples were processed through fixation, dehydration, paraffin embedding, and sectioning at a thickness of 5 μm. The tissue sections were then stained using the hematoxylin and eosin (H&E) method.

2.8 Histopathological and Morphometric Assessment

Histological sections were examined using an Olympus CX-33 microscope equipped with an Olympus DP22 digital camera at 10× and 40× magnifications. Pancreatic islet morphology and area were evaluated in five fields of view per sample, with each field representing an image area of 1 mm². The archived experimental records did not specify the image-analysis software or exact calculation procedure used for islet area, the precise procedure used to select the five fields of view, or whether the morphometric assessment was performed blinded to experimental group allocation; therefore, these methodological details could not be retrospectively verified.

2.9 Statistical Analysis

Before statistical analysis, the collected data underwent editing, coding, entry, and cleaning procedures. Statistical analysis was performed using STATA software. Data normality was assessed using the Shapiro–Wilk test. Day-28 random blood glucose levels were analyzed using the Kruskal–Wallis test, followed by Bonferroni-adjusted Mann–Whitney U tests for pairwise comparisons. Pancreatic islet area was

analyzed using one-way ANOVA followed by the Bonferroni post hoc test. A p-value < 0.05 was considered statistically significant.

3.Results

This study involved 21 male Sprague-Dawley rats that were randomly divided into three groups: negative control group, diabetic control group, and secretome-treated diabetic group, with seven rats in each group. All animals completed the study period, which consisted of one week of acclimatization followed by a four-week experimental period. No dropouts were recorded during the study.

At day 28, the diabetic control group had the highest mean random blood glucose level (423.00 ± 36.89 mg/dL), followed by the secretome-treated diabetic group (263.71 ± 122.29 mg/dL), whereas the negative control group had the lowest mean level (106.85 ± 4.52 mg/dL).

The mean pancreatic islet area was largest in the negative control group (16,650.15 ± 6,042.75 μm²), followed by the secretome-treated diabetic group (12,939.40 ± 6,487.93 μm²), whereas the diabetic control group had the smallest mean islet area (5,353.93 ± 3,131.48 μm²) (Table 1).

Table 1. Descriptive Characteristics of Day-28 Random Blood Glucose Levels and Pancreatic Islet Area

Variable	Group	n	Mean	SD	Min.	Max.
Day-28 random blood glucose	Negative control	7	106.85	4.52	98	112
Day-28 random blood glucose	Diabetic control	7	423.00	36.89	357	463
Day-28 random blood glucose	Secretome-treated diabetic	7	263.71	122.29	143	412
Pancreatic islet area (μm²)	Negative control	7	16,650	6,042	9,746	26,924
Pancreatic islet area (μm²)	Diabetic control	7	5,353	3,131	3,436	12,106
Pancreatic islet area (μm²)	Secretome-treated diabetic	7	12,939	6,487	6,913	24,752

The Kruskal–Wallis test showed a significant difference in day-28 random blood glucose levels among the three groups (p = 0.0003). Pairwise comparisons using the Mann–Whitney U test with Bonferroni adjustment showed significant differences between the negative control and diabetic control groups (adjusted p = 0.0051), the negative control and secretome-treated diabetic groups (adjusted p = 0.0051), and the diabetic control and secretome-treated diabetic groups (adjusted p = 0.0378). Thus, the secretome-treated diabetic group had significantly lower day-28 random blood glucose than the untreated diabetic control group, although glucose remained higher than in the negative control group (Tables 2 and 3).

Table 2. Kruskal–Wallis Test of Day-28 Random Blood Glucose Levels

Group	n	Rank Sum	p value
Negative control	7	28.00	
Diabetic control	7	121.00	0.0003
Secretome-treated diabetic	7	82.00	

Table 3. Post Hoc Mann–Whitney U Test of Day-28 Random Blood Glucose Levels

Comparison	Day-28 Random Blood Glucose, Mean ± SD	p value	Adjusted p-value*
Negative control vs diabetic control	106.85 ± 4.52 vs 423.00 ± 36.89	0.0017	0.0051
Negative control vs secretome-treated diabetic	106.85 ± 4.52 vs 263.71 ± 122.29	0.0017	0.0051
Diabetic control vs secretome-treated diabetic	423.00 ± 36.89 vs 263.71 ± 122.29	0.0126	0.0378

*Adjusted p-values were calculated using the Bonferroni correction.

One-way ANOVA showed a significant overall difference in pancreatic islet area among the three groups (p = 0.0043). The Bonferroni post hoc test showed a significant difference between the negative control and diabetic control groups (p = 0.004). No significant difference was observed between the negative control and secretome-treated diabetic groups (p = 0.687). The secretome-treated diabetic group had a descriptively larger mean islet area than the diabetic control group, but this comparison did not reach statistical significance (p = 0.061) (Tables 4 and 5).

Table 4. One-Way ANOVA of Mean Pancreatic Islet Area

Group	Mean (μm²)	SD	p value
Negative control	16,650.15	6,042.75	
Diabetic control	5,353.93	3,131.48	0.0043
Secretome-treated diabetic	12,939.40	6,487.93	

Table 5. Bonferroni Post Hoc Test of Pancreatic Islet Area

Comparison	Pancreatic Islet Area, Mean ± SD (μm²)	p value
Negative control vs diabetic control	16,650.15 ± 6,042.75 vs 5,353.93 ± 3,131.48	0.004
Negative control vs secretome-treated diabetic	16,650.15 ± 6,042.75 vs 12,939.40 ± 6,487.93	0.687
Diabetic control vs secretome-treated diabetic	5,353.93 ± 3,131.48 vs 12,939.40 ± 6,487.93	0.061

Histopathological examination of the negative control group showed preserved pancreatic islet architecture with compact cellular organization and a representative islet area of approximately 16,260.10 μm². In contrast, the diabetic control group showed

reduced islet area, decreased cellular density, disrupted cellular organization, and degenerative morphological changes compatible with cellular injury, with a representative islet area of approximately 5,351.73 μm². The secretome-treated diabetic group showed better-preserved islet morphology and a more organized cellular arrangement than the diabetic control group, with a representative islet area of approximately 14,378.67 μm². These descriptive histological findings were consistent with the larger mean islet area observed in the secretome-treated group; however, the secretome-versus-diabetic-control difference did not reach statistical significance ($p = 0.061$).

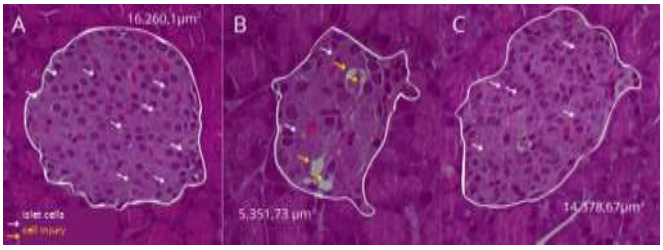

Figure 1. Comparison of the Area of the Islets of Langerhans at 40× Magnification.

The negative control group (A) shows preserved pancreatic islet architecture with compact cellular organization and a representative area of 16,260.10 μm². The diabetic control group (B) shows reduced islet area, decreased cellular density, disrupted organization, and degenerative morphological changes compatible with cellular injury, with a representative area of 5,351.73 μm². The secretome-treated diabetic group (C) shows better-preserved islet morphology and a more organized cellular arrangement, with a representative area of 14,378.67 μm². H&E staining was used; therefore, these observations should not be interpreted as direct evidence of β-cell-specific apoptosis or regeneration. White arrows indicate representative islet cells, whereas yellow arrows indicate morphological changes compatible with cellular injury.

4. Discussion

This study aimed to evaluate the effects of mesenchymal stem cell (MSC)-derived secretome administration on day-28 random blood glucose levels and pancreatic islet morphology in STZ-induced diabetic rats. The secretome-treated diabetic group showed significantly lower day-28 random blood glucose than the untreated diabetic control group. Pancreatic islet area differed significantly among the three groups overall; however, the difference between the diabetic control and secretome-treated diabetic groups did not reach statistical significance. The histological findings therefore support a cautious interpretation of better-preserved islet morphology rather than direct evidence of β-cell regeneration.

In diabetes mellitus, persistent hyperglycemia can promote oxidative stress, inflammatory signaling, and pancreatic islet injury. STZ is preferentially taken up by pancreatic cells through GLUT2 and produces cytotoxic injury that contributes to hyperglycemia and structural damage to the islets. In the present study, the experimental phenotype was established by persistent hyperglycemia and pancreatic islet injury. Because insulin resistance was not directly assessed and no high-fat diet or nicotinamide was used, this model should be interpreted as an STZ-induced diabetic model rather than a definitive experimental model of type 2 diabetes mellitus [11,12].

The present study demonstrated significant differences in day-28 random blood glucose levels among the experimental groups. The diabetic control group showed the highest mean value (423.00 ± 36.89 mg/dL), whereas the secretome-treated diabetic group had a lower mean value (263.71 ± 122.29 mg/dL). The Bonferroni-adjusted pairwise comparison between these groups was significant (adjusted $p = 0.0378$). This finding indicates an association between repeated UCMSC-derived secretome administration and improved glycemic control in this experimental setting. However, insulin concentrations, insulin sensitivity, and glucose tolerance were not directly assessed; therefore, the mechanism underlying the lower glucose level cannot be determined from the present data.

Histological analysis using H&E staining showed that STZ-induced diabetes was associated with reduced pancreatic islet area, decreased cellular density, disrupted cellular organization, and degenerative morphological changes compatible with cellular injury. The secretome-treated diabetic group showed a larger mean islet area and better-preserved morphology than the diabetic control group. Nevertheless, the difference in islet area between these two groups did not reach statistical significance ($p = 0.061$). Because H&E staining does not specifically identify β-cells or establish apoptosis, these findings should be interpreted as morphological preservation or improvement of islet architecture rather than direct evidence of β-cell regeneration or reduced apoptosis.

The UCMSC-derived secretome used in this study was obtained as a prepared product from Regenic, PT Bifarma Adiluhung, Indonesia. Manufacturer-provided characterization documented measurable concentration ranges for bFGF, TGF-β1, KGF, HGF, and procollagen I alpha 1, while multiple additional cytokines, chemokines, growth-related proteins, and other bioactive substances were qualitatively identified. These components provide biological plausibility for paracrine and tissue-protective effects reported for MSC-derived secretome in the literature [6,7,14]. However, the present study did not experimentally determine which individual secretome component, or combination of components, was responsible for the observed glycemic or morphological findings.

The documented product composition should therefore be interpreted as manufacturer-provided characterization rather than as a mechanistic assay performed within this experiment. The concentration ranges were derived from manufacturer testing conducted between 2020 and September 2023 and were not batch-specific measurements generated for the animals in the present study. Consequently, mechanistic

explanations based on individual growth factors or cytokines remain hypotheses supported by prior literature rather than direct molecular evidence from this experiment.

This study has several limitations. First, the relatively short observation period and small sample size may have limited the ability to detect more pronounced structural differences in pancreatic islets. Second, we did not assess insulin concentration, insulin resistance, glucose tolerance, and specific β-cell markers such as insulin expression, PDX-1, Ki-67, and β-cell mass. Third, H&E staining alone cannot specifically identify β-cells or definitively establish apoptosis; therefore, the histological findings are limited to morphological descriptions of islet architecture and cellular injury. Fourth, although manufacturer-provided compositional data were available for the UCMSC-derived secretome, detailed information regarding MSC passage, culture and conditioning conditions, secretome collection and processing, storage conditions, and batch-specific characterization was not available. Fifth, the archived records did not specify the image-analysis software or exact area-calculation procedure, the precise method used to select the five fields of view, or whether morphometric assessment was blinded to experimental group allocation. Finally, because the model was induced using a single dose of STZ without a high-fat diet, nicotinamide, or direct assessment of insulin resistance, it should be interpreted as an STZ-induced diabetic model rather than a definitive model of type 2 diabetes mellitus. Future studies should incorporate longer follow-up, standardized and batch-specific secretome characterization, predefined blinded morphometric procedures, and molecular and functional measures of pancreatic endocrine recovery.

5. Conclusion

This study demonstrated that repeated MSC-derived secretome administration was associated with lower day-28 random blood glucose levels in STZ-induced diabetic Sprague-Dawley rats compared with untreated diabetic controls. Pancreatic islet area differed significantly among groups overall, but the secretome-treated diabetic group did not differ significantly from the diabetic control group in the pairwise comparison ($p = 0.061$). H&E examination showed better-preserved islet morphology in the secretome-treated group; however, these findings do not constitute direct evidence of β-cell regeneration or apoptosis. Further studies incorporating β-cell-specific markers, functional metabolic assessments, longer follow-up, and standardized secretome characterization are warranted.

Declarations

Author Contributions

Conceptualization, Jonathan Gerwyn and Tena Djuartina; methodology, Jonathan Gerwyn, Tena Djuartina, Robi Irawan, and Veronika Maria Sidharta; validation, Tena Djuartina, Iskandar Rahardjo Budianto, Robi Irawan, and Veronika Maria Sidharta; formal analysis, Jonathan Gerwyn; investigation, Jonathan Gerwyn; data curation, Jonathan Gerwyn, Tena Djuartina; writing original draft preparation, Tena Djuartina, Iskandar Rahardjo Budianto, Robi Irawan, and Veronika Maria Sidharta; visualization, writing review and editing Jonathan Gerwyn, Tena Djuartina; supervision, Tena Djuartina and Iskandar Rahardjo Budianto; project administration, Tena Djuartina; funding acquisition, Jonathan Gerwyn. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

The data supporting the findings of this study are contained within the article. Additional data are available from the corresponding author upon reasonable request.

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Institutional Review Board Statement

The animal study protocol was submitted for ethical review on 26 July 2025 and approved on 8 August 2025 by the Research Ethics Committee of the School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, Jakarta, Indonesia (Approval No. 02/08/KEP-FKIKUAJ/2025). All procedures involving animals were initiated only after this approval had been granted.

Animal Ethics Statement

All animal procedures were initiated only after ethical approval had been granted on 8 August 2025. No animal experimentation was conducted before approval. All procedures were performed in accordance with applicable institutional guidelines and the principles of Replacement, Reduction, and Refinement (3Rs).

Conflicts of Interest
The authors declare no conflicts of interest.

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